REMARKS

I. Status Summary

Claims 1-60 are pending in the present application. Claims 5-60 have been withdrawn pursuant to a Restriction/Election Requirement issued by the U.S. Patent Office. Claims 1-4 are currently under examination.

Claims 1-4 are rejected under 35 USC § 112, first paragraph, upon the contention that the claims fail to comply with the written description requirement.

Claims 1-4 are rejected under 35 USC § 112, first paragraph, upon the contention that the claims fail to comply with the enablement requirement.

Claim 2 has been amended. Support for the amendment to claim 2 can be found throughout the specification as filed, including particularly at page 6, lines 14-26; page 10, line 28, through page 11, line 2; page 15, lines 9-11; in Figure 1; and in the Sequence Listing. No new matter has been added.

Reconsideration of the application based on the arguments set forth herein is respectfully requested.

II. Response to the Rejections under 35 U.S.C. § 112, Second Paragraph.

Claims 1-4 are rejected under 35 USC § 112, first paragraph, upon the contention that the claims fail to comply with the written description requirement as well as the enablement requirement.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

II.A. Written Description

The Patent Office contends that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Patent Office contends that the claims do not set forth any structural requirements for biologically active heparan sulfate 3-*O*-sulfotransferase-5 polypeptide (hereinafter "3-OST-5"), including the amino acid residues required for the enzymatic activity. As such, the Patent Office

contends that the specification does not support the genus of polypeptide molecules encoded by the enormous number of nucleotide molecules. Thus, the Patent Office alleges that at the time of filing, only heparan sulfate 3-*O*-sulfotransferase-5 polypeptide isolated from human was disclosed.

Initially, applicants respectfully submit that the Patent Office's position that the claims fail to meet the written description requirement appears to be based upon the contention that the specification fails to adequately describe the structural characteristics of 3-OST-5 that impart a function to 3-OST-5. *See*, e.g., page 11 of the Official Action, which states, "The important information missing to suffice the broad genus as claimed is the demonstration of the domain structure required for the binding to the substrate of the 3-OST-5, and the domain structure required for the binding to the HSV-1 glycoprotein D (gD) of the 3-OST-5." and "Furthermore, the specification does not provide any structure of 3-OST-5 required for the binding to the HSV-1 glycoprotein D (gD), which is encompassed by the broad genus of the biological activity of 3-OST-5 polypeptide.".

In response, applicants first note that the Patent Office appears to have mischaracterized the function of 3-OST-5, as 3-OST-5 does not have a function of binding to HSV-1. Rather, in some embodiments, 3-OST-5 can modify a heparan sulfate (HS) molecule such that the modified HS can act as a receptor for HSV-1. Stated another way, 3-OST-5 is capable of assisting the entry of HSV-1 by generating a receptor for gD, the receptor being a 3-OST-5 modified HS. *See*, e.g., page 77, line 11, through page 78, line 23, of the instant specification. Accordingly, applicants respectfully submit that the Patent Office's contention that the specification does not provide any structure of 3-OST-5 required for the binding to HSV-1 gD, upon which the written description rejection is based, is inaccurate.

Furthermore, the Patent Office contends that alignment of amino acid sequences between 3-OST-1, 3-OST-3, and 3-OST-5 for the identification of putative sulfotranferase domains is not sufficient to meet the requirement for written description. This contention appears to be based upon the suggestion that the tertiary structure of 3-OST-5 is required to satisfy the written description requirement. *See* page 11 of the Official Action. However, applicants respectfully submit that no

such requirement is believed to exist. Rather, the Patent Office appears to have selected a single sentence within the specification as a basis for this alleged requirement. Namely, the specification, at page 17, lines 3-5, at best, impliedly states that the substrate specificities of 3-OST isoforms may be determined by the three-dimensional structures of the enzymes. However, this statement does not suggest that determining tertiary structure is required. Further, selecting a single sentence fails to consider the teachings of the specification as a whole. As such, it is believed to be improper to require the applicants to provide the tertiary structure of 3-OST-5 in order to satisfy the written description requirement based solely upon this statement.

Additionally, applicants respectfully direct the Patent Office to the Technical Note (**Exhibit B**) incorporated in Example 11, page 38, of the Written Description Training Materials (Revision 1; March 25, 2008; hereinafter "the WDTM"). In particular, the Technical Note states, "Generally, tertiary structure conservation would be lost when the amino acid sequence varies by more than 50%.". Applicants respectfully submit that rejected claims 1-4 recite 95% sequence identity. As such, the claimed genus of 3-OST-5 varies from SEQ ID NO 2 by 5%, at most. Therefore, as would be appreciated by one of ordinary skill in the art, if the tertiary structure of a protein can be conserved when the amino acid sequence varies by as much as 50%, as suggested by the Patent Office, it logically follows that the tertiary structure would very likely be conserved in a protein with less than 5% sequence variation.

Finally, the Patent Office appears to have dismissed applicant's previous arguments based upon the holdings in *Enzo Biochem Inc.* v. *Gen-Probe Inc.,* 296 F.3d 1316,63 U.S.P.Q.2d 1609 (Fed. Cir. 2002) and *Ex parte Jon Elliot Adler*, Appeal No. 2006-0157 (2006) (hereinafter "*Adler*"; provided as **Exhibit A** in the response of January 14, 2008), upon the contention that status of the art of the subject matters is different. *See*, page 12 of the instant Official Action. The Patent Office again bases this contention on the assertion that the biological activity of 3-OST-5 is dependent upon the tertiary structure of the protein. Thus, based upon the discussion hereinabove regarding tertiary structure, it appears that the previous arguments based upon *Enzo* and *Adler* were improperly dismissed and not given adequate

consideration. As such, applicants respectfully request that the arguments based upon *Enzo* and *Adler* be reconsidered. These arguments have been summarized herein for convenience and completeness.

The Federal Circuit in *Enzo* held that a description *of functional characteristics of a claimed compound, coupled with a known or disclosed correlation between function and structure,* may adequately describe a claimed invention. *See Enzo, 63* U.S.P.Q.2d at 1613 (emphasis in original); *cf In re Robins,* 429 F.2d 452,166 U.S.P.Q. 552, 555 (C.C.P.A. 1970) ("Mention of representative compounds encompassed by generic claim language clearly is not required by §112 or any other provision of the statute."). The *Enzo* Court specifically stated that a compound may be adequately described by "stringent hybridization" to a known sequence because "such conditions dictate that all species within the genus will be structurally similar." *Enzo,* 63 U.S.P.Q.2d at 1615. Applicants provide such a description of the structural similarity of 3-OST-5 polypeptides coupled with functional characteristics and a known correlation between function and structure.

Applying the *Enzo* principles to the present case, the claimed genus of biologically active 3-OST-5 polypeptides are structurally related. Just like nucleic acids that hybridize under high stringency to a known sequence are structurally similar (*see Enzo* above); it reasonably follows that the proteins encoded by the nucleic acids are also structurally related. Likewise, polypeptides having greater than 95% sequence identity to a known sequence are highly structurally related to the known sequence. Therefore, the claimed genus of 3-OST-5 polypeptides having greater than 95% sequence identity to SEQ ID NO 2, encoded by a nucleic acid having greater than 95% sequence identity to SEQ ID NO 1 or encoded by a nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule of SEQ ID NO 1 are structurally similar.

In view of the known correlation between protein structure and function, it reasonably follows that structurally similar proteins are also functionally related. The protein structure-function relationship can be illustrated by the 3-OST isozymes in the instant case. For example, the 3-OST-1, 3-OST-3 and 3-OST-5 isozymes have similar activities in that they all attach sulfate to heparin sulfate. However, the

isozymes show differences in substrate preference, which manifests in different biological functions. *See,* for example, the specification at pages 16-17, lines 28-32 and 1-10, respectively. The 3-OST-1 and 3-OST-3 isozymes are 72% and 58% identical, respectively, to the 3-OST-5 isozyme in the sulfotransferase domain. *See, Instant Specification*, page 16, lines 14-16. Given that the 3-OST-1 and 3-OST-3 isozymes have similar activity to 3-OST-5 but a relatively low degree of sequence identity (72% and 58%, respectively), the claimed genus of polypeptides having greater than 95% sequence identity to 3-OST-5 can be expected to have even greater functional similarity.

In light of the foregoing, the claimed genus of biologically active 3-OST-5 polypeptides is adequately described by reference to the single example of the protein of SEQ ID NO 2. Applicants provide measurable identifying functional characteristics of the claimed genus of biologically active 3-OST-5 polypeptides, the claimed genus of polypeptides is structurally similar to the 3-OST-5 polypeptide of SEQ ID NO 2, and there is a known correlation between polypeptide structure and function. Therefore, applicants have provided sufficient written description of the claimed genus of biologically active 3-OST-5 polypeptides and the rejection under 35 U.S.C. § 112, first paragraph, on the basis of a lack of written description, should be withdrawn.

Applicants further submit that the instant rejection of a genus of highly structurally related polypeptides where there is a disclosed assay for measuring function is believed to be in conflict with *Adler*. One question at issue in the *Adler* case was whether a claimed genus of nucleotide sequences encoding bitter taste receptors met the requirements of 35 U.S.C. § 112, first paragraph. The Board of Patent Appeals and Interferences in *Adler* held as being adequately described and enabled, claims to nucleotide sequences encoding bitter taste receptor polypeptides having at least 95% sequence identity to a specific bitter taste receptor polypeptide or that hybridize under stringent conditions to a specific nucleotide sequence encoding the bitter taste receptor.

In the *Adler* case, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, was stated as follows: "the claims encompass polynucleotides not described in the specification, e.g., mutated sequences, allelic variants, or sequences that have a recited degree of identity. None of these sequences meet the written description provision of 35 U.S.C. § 112, first paragraph." In its response, the court cited *Enzo* for the proposition that "the written description can be met by showing . . . relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Ex parte Jon Elliot Adler* citing *Enzo*, 63 U.S.P.Q.2d at 1613 (emphasis omitted). In its holding, the Board of Patent Appeals and Interferences stated: "The claims are limited to nucleic acids that hybridize under stringent conditions to SEQ ID NO:7 or that encode polypeptides at least 95% identical to SEQ ID NO:8. Thus, the claimed nucleic acids will necessarily have a high degree of structural similarity to SEQ ID NO:7 . . .". The court went on further to say that while the specification did not allow those skilled in the art to know without testing which of the hybridizing or 95% identical sequences would encode polypeptides with the receptor function, the disclosure in the specification of an assay that could be used by one skilled in the art to determine function was sufficient written description for the claims to be found allowable.

The facts in the instant application are very close to those in *Adler*. The claims are similarly drawn to 3-OST-5 polypeptides having greater than 95% sequence identity to a specific 3-OST-5 polypeptide sequence, and an assay is provided in the instant specification for detecting 3-OST-5 activity. Applicants provide measurable identifying functional characteristics of the claimed genus of biologically active 3-OST-5 polypeptides, the claimed genus of polypeptides is structurally similar to the 3-OST-5 polypeptide of SEQ ID NO 2, and there is a known correlation between polypeptide structure and function. Therefore, the genus of biologically active 3-OST-5 polypeptides encompassed by amended claims 1-4 is adequately described by reference to the specific protein of SEQ ID NO 2. *See Enzo,* 63 U.S.P.Q.2d at 1615. The Patent Office has not shouldered its burden of presenting evidence to the

contrary. *See In re Detiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). The elements of a high level of structural similarity and assays for measuring function would have allowed a person of ordinary skill in the art to recognize the genus of polypeptides being claimed, and recognition of what is being claimed suffices for compliance with the written description requirement. Accordingly, applicants have provided sufficient written description of the claimed genus of biologically active 3-OST-5 polypeptides and respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, on the basis of a lack of written description.

Continuing with the instant rejection, applicants respectfully submit that claims 1-4 are also believed to satisfy the written description requirements based upon Example 11 of the the WDTM. In the instant Official Action the Patent Office directs applicant's attention to Example 11A. The Patent Office contends that Example 11A provides the appropriate analysis based upon the assertion that no structure-function correlation is present in the instant application. However, as discussed hereinabove, applicants respectfully submit that a structure-function relationship is believed to be disclosed and should not be negated for an asserted failure to disclose details of the tertiary structure of 3-OST-5. As such, the analysis in Example 11B of the WDTM is believed to be more appropriate for the presently disclosed and claimed subject matter as the facts of Example 11B appear to more closely parallel the instant disclosure.

In particular, the disclosure in Example 11B includes a single nucleotide sequence, a single peptide sequence, and data identifying two domains relevant to a specified activity of the peptide. Likewise, the instant disclosure includes a polynucleotide sequence (SEQ ID NO 1), the peptide sequence for 3-OST-5 (SEQ ID NO 2) encoded by SEQ ID NO 1, and conserved binding domains identified as 3'-PSB and 5'-PSB (Figure 2). Additionally, unlike Example 11B, the instant disclosure also sets forth assays for detecting biologically active variants of the claimed peptide. Furthermore, presently rejected claims 1-4 recite 95% sequence identity whereas the claims of Example 11B recite only 85% sequence identity.

Therefore, the instant disclosure closely parallels and includes at least each and every disclosed feature of Example 11B. Example 11B concludes that the specification satisfies the written description requirements with respect to both claims 1 and 2 set forth in Example 11B. Accordingly, given that the instant disclosure closely tracks that of Example 11B it is believed to be in compliance with the written description requirements as it pertains to claims 1-4.

Taken together, applicants respectfully submit that the instant disclosure is believed to be in compliance with the written description requirements under 35 U.S.C. § 112, first paragraph, with respect to claims 1-4. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 1-4 under 35 USC § 112, first paragraph. Applicants respectfully request a Notice of Allowance of claims 1-4.

II.B. Enablement

Claims 1-4 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirements. The Patent Office appears to be alleging that the specification enables only a nucleic acid encoding the 3-OST-5 polypeptide of SEQ ID NO 2. Applicants respectfully submit that the specification enables at least the genus of biologically active and structurally related 3-OST-5 polypeptides of claims 1-4.

Similar to the written description rejection discussed hereinabove, the Patent Office appears to have based the instant enablement rejection on the contention that the alignment of amino acid sequences between 3-OST-1, 3-OST-3, and 3-OST-5 for the identification of putative sulfotranferase domains is not sufficient to establish a structure-function relationship and satisfy the enablement requirements. This contention appears to be based upon the further contention that the tertiary structure of 3-OST-5 is required to satisfy the enablement requirement. *See* page 20 of the Official Action. However, applicants respectfully submit that no such requirement is believed to exist and that the Patent Office appears to have offered only a single sentence within the specification as a basis for this alleged requirement. As discussed hereinabove with respect to the written description rejection, the specification, at best, impliedly states that the substrate specificities of 3-OST isoforms may be determined by the three-dimensional structures of the enzymes.

Based upon this single statement in the specification, the Patent Office asserts that "this conservation [referring to conserved regions between 3-OST-1, 3-OST-3, and 3-OST-5] is not correlated with function because the specification disclose[s] three-dimensional structure is critical for substrate recognition and binding" (*see*, page 20 of the instant Official Action; emphasis added). However, applicants respectfully submit that the Patent Office appears to have overstated and overemphasized the statement in the specification regarding tertiary structure.

Additionally, applicants again respectfully direct the Patent Office to the Technical Note at page 38 of the WDTM, which indicates that the tertiary structure of a protein can be conserved when the amino acid sequence varies by as much as 50%. Thus, even assuming *arguendo* that the tertiary structure of the claimed 3-OST-5 is relevant to its function, the tertiary structure of the claimed genus of 3-OST-5 would very likely be conserved given that the claimed genus have less than 5% variation from SEQ ID NO 2. Taken together, it is believed to be improper to require applicants to provide the tertiary structure of 3-OST-5 in order to satisfy the enablement requirement based solely upon the statement mentioned above.

Continuing with the instant rejection, applicants respectfully submit that claims 1-4 are believed to be enabled in view of the disclosed and claimed subject matter. In particular, the genus of the claimed 3-OST-5 is at least 95% identical to SEQ ID NO 2, and the specification discloses the complete sequence of nucleic acids encoding the protein of SEQ ID NO 2, assays to determine whether the modified protein possesses 3-OST-5 activity (*see, e.g.,* Examples 2-9), and guidance to make the appropriate amino acid modifications provided by the sequence comparison in Figure 2 showing conserved and less conserved regions between the 3-OST isozymes, 3-OST-1, 3-OST-3A, 3-OST-3B and 3-OST-5.

Additionally, one of ordinary skill in the art appreciates that limited amino acid alterations, *e.g.,* a single amino acid modification, *generally* can be made with a reasonable expectation of maintaining protein function. Gassner *et al., Proc. Nat'l Acad. Sci USA* 93: 12155-58 (1996); (hereinafter "*Gassner et al.*"; provided as **Appendix A** in the response of January 14, 2008) reveals that considerable (up to 10) amino acid alterations can be made even to the tightly packed core of a globular

protein without eliminating activity or folding of the protein. Wells, *Biochemistry* 29: 8509-17 (1990) (hereinafter "*Wells*"; provided as **Appendix B** in the response of January 14, 2008) discloses that the free energy changes in mutant proteins *generally* are additive with increasing numbers of amino acid mutations. Further, some experimentation to determine which embodiments encompassed by the claims will work is permitted without the experimentation being undue in nature. *See Angstadt, 190* U.S.P.Q. at 218; *Wands,* 858 F.2d 736-37 ("Enablement is not precluded by the necessity for some experimentation such as routine screening."). Accordingly, in contrast to the assertions by the Patent Office, the experimentation required to make and use the genus of biologically active 3-OST-5 polypeptides of claims 1-4 is not undue, as it is routine in nature and the required techniques are well known to the skilled artisan.

Furthermore, the routine nature of the experimentation required to practice the full scope of the instant claims is supported by the holding in *Alder*. As described above for written description, in *Adler* the court held as being adequately described and enabled, claims to nucleotide sequences encoding bitter taste receptor polypeptides having at least 95% sequence identity to a specific bitter taste receptor polypeptide or that hybridize under stringent conditions to a specific nucleotide sequence encoding the bitter taste receptor. On facts very similar to those in the instant case, the court in *Adler* found the Examiner had not adequately explained why practicing the full scope of the claims would have required undue experimentation. The *Adler* court found that undue experimentation would not be required to make and use the claimed genus of bitter taste receptors. In its decision, the court stated that the specification provides the nucleotide and amino acid sequences for the human bitter taste receptor. The court went on to say that the specification also discloses an amino acid sequence comparison of twenty three human, mouse and rat bitter taste receptors that identifies conserved and less conserved regions, thereby providing guidance to those skilled in the art regarding what regions are likely to be required for function. According to the *Adler* court, it is known in the art that changes in conserved regions are more likely to disrupt function of the protein than changes in non-conserved regions. Thus, the court stated that the

Adler specification guides a skilled worker to areas of the bitter taste receptors that are likely to be tolerant to amino acid changes.

The court in *Adler* also pointed out that the specification discloses assays for determining whether a particular bitter taste receptor retains the activity of the wild-type protein. In its holding, the court based its finding that the Examiner failed to show nonenablement by a preponderance of evidence on 1) the prior art providing substantial guidance with respect to the direction the experimentation should proceed; 2) a process being provided for making and assaying the mutated proteins (noting the process "to be routine, if tedious, experimentation"); and 3) the claimed genus being limited to variants having 95% or less variation compared to the wild-type sequence or hybridizing under stringent conditions to the nucleic acid encoding the wild-type protein.

Similar to the *Adler* case, the instant specification provides the nucleotide and amino acid sequences shown in SEQ ID NOs 1 and 2, corresponding to human 3-OST-5. The instant specification also discloses an amino acid sequence comparison of the 3-OST-1, 3-OST-3A, 3-OST-3B and 3-OST-5 isozymes showing conserved and less conserved regions, thereby providing guidance to those skilled in the art regarding what regions are likely to be required for function and less tolerant to amino acid changes. *See* Figure 2. Like in *Adler*, the instant specification discloses assays for determining whether a particular 3-OST-5 polypeptide retains the activity of the wild-type protein. *See* Examples 1-9. Accordingly, like in the *Adler* case, the experimentation required to make and use the genus of biologically active 3-OST-5 polypeptides of amended claims 1-4 is not undue, as it is routine in nature and the required techniques are well known to the skilled artisan.

Taken together, applicants respectfully submit that claims 1-4 are believed to be enabled and therefore in compliance with 35 U.S.C. § 112, first paragraph. Accordingly, applicants respectfully request withdrawal of the rejection of claims 1-4 under 35 USC § 112, first paragraph. Applicants respectfully request a Notice of Allowance of claims 1-4.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayment associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

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421/67 PCT/US AAT/LRL/cam

Exhibit B

nus of nucleic acids that encode SEQ ID NO: 2. With the aid of a computer, one of skill in the art could have identified all of the nucleic acids that encode a polypeptide with at least 85% sequence identity with SEQ ID NO: 2. Thus, one of ordinary skill in the art would conclude that the applicant was in possession of the claimed genus at the time the application was filed.

Conclusion:

The specification satisfies the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the scope of claim 1.

Claim 2

Claim 2 encompasses nucleic acids that encode the polypeptide of SEQ ID NO: 2, and nucleic acids that encode a polypeptide having 85% sequence identity to SEQ ID NO: 2 and have activity X. The specification discloses the reduction to practice of only a single species that encodes SEQ ID NO: 2 and has activity X; *i.e.*, SEQ ID NO: 1. There are no other drawings or structural formulas disclosed of a nucleic acid that encodes either SEQ ID NO: 2 or a polypeptide having 85% sequence identity to SEQ ID NO: 2 and activity X.

The claim includes a genus that can be analyzed at several levels sequentially for the purpose of focusing the issue.

First, the disclosure of SEQ ID NO: 2 combined with pre-existing knowledge in the art regarding the genetic code and its redundancies would have put one in possession of the genus of nucleic acids that encode SEQ ID NO: 2. With the aid of a computer, one of skill in the art could identify all of the nucleic acid sequences that encode a polypeptide with at least 85% sequence identity with SEQ ID NO: 2. However, there is no teaching regarding which 15% of the amino acids can vary from SEQ ID NO: 2 and still result in a protein that retains activity X. Further, there is no disclosed or art-recognized correlation between any structure other than SEQ ID NO: 2 and novel activity X.

An important consideration is that structure is not necessarily a reliable indicator of function. In this example, there is no disclosure relating similarity of structure to conservation of function. General knowledge in the art included the knowledge that some amino acid varia-

TECHNICAL NOTE

For information on amino acid substitution exchange groups and empirical similarities between amino acid residues, see a standard text such as Schulz et al., PRINCIPLES OF PROTEIN STRUCTURE, pp. 14-16, Springer-Verlag (New York 1979). There is a limit to how much substitution can be tolerated before the original tertiary structure is lost. Generally, tertiary structure conservation would be lost when the amino acid sequence varies by more than 50%. See, e.g., Cyrus Chothia and Arthur M. Lesk, "The relation between the divergence of sequence and structure in proteins," 5 THE EMBO JOURNAL 823-26 (1986).